



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

February 26, 2001

MEMORANDUM

SUBJECT: Butylate. (Chemical ID No. 041405, Case No. 0071). HED Revised Human Health Assessment. No MRID #. DP Barcode No. D248405.

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This memorandum and attachments update the Health Effects Division Reregistration Eligibility Decision Document (HED RED) for Butylate (Charles Frick, 7/27/93) taking into consideration requirements of the 1996 Food Quality Protection Act (FQPA). An Agency RED for butylate was previously issued November 1993. Few changes have been made to butylate from a human health standpoint since the issuance of the RED. Changes in the 40 CFR §180.232 to replace the chemical name "S-ethyl diisobutylthiocarbamate" with the acceptable common name "butylate", deleting the term negligible residues from the tolerance expression, and modifications to reflect current commodity definitions were done as recommended in the previous RED chapter. A Tolerance Reassessment Eligibility Decision (TRED) document is required since EPA completed the RED for butylate before passage of the FQPA. This assessment only discusses the human health risk assessment required for reassessment of tolerances and does not include an occupational risk assessment required for reregistration of products. Cumulative risk assessment considering risks from other pesticides which have a common mechanism of toxicity is also not addressed in this document. Attachments include the most recent Hazard Identification Review Committee (HIARC) report (attachment 1, Paul Chin, 8/7/98), and the most recent dietary risk analysis (attachment 2, Felecia Fort, 1/22/01).

1.0 EXECUTIVE SUMMARY

Butylate (S-ethyl diisobutylthiocarbamate) is a member of the thiocarbamates group of herbicides, that include molinate and pebulate. It is currently registered for use only on field corn, sweet corn, and popcorn. It is used in the form of an emulsifiable concentrate and granules. Butylate in the past has also been formulated with atrazine but that formulation has been phased out. Butylate is a highly volatile. Consequently, it is applied with ground equipment and is incorporated into the soil immediately after application. The toxicity and residue chemistry databases for butylate are complete and support reregistration eligibility. Human health risks are considered to be minimal due to its low toxicity (acute categories III and IV), its classification as a Group E "not likely" carcinogen and its low dietary risk.

Submitted subchronic toxicity studies indicated no significant toxicity while chronic toxicity studies showed butylate decreased body weight and caused some changes in the liver pathology. Butylate produced developmental toxicity (decreased fetal body weight and an increase in anatomical variations) in rats but did not affect the reproductive parameters. Butylate is not a mutagen, and metabolism studies indicate that there was no evidence of bioaccumulation and no metabolites found which raised toxicological concern. Clinical and neurotoxic effects (induced neuronal cell necrosis in the brain and degeneration of sciatic nerve) were seen only at the high dose (2000 mg/kg) level in the acute neurotoxicity study; no neurotoxic effects were seen in the subchronic neurotoxicity study which tested substantially lowered doses. Additionally, there were no compound-related changes recorded in brain, plasma or erythrocyte cholinesterase activities. When considering chronic exposure, HED selected an endpoint based on liver clinical chemistry effects. Acute endpoints were also selected for females of child-bearing age based on developmental effects and for the general population based on acute neurotoxic effects and clinical signs.

The FQPA required the Agency to consider potential special sensitivity to infants and children from exposure to butylate. Submitted toxicity studies showed that there is no increased sensitivity or susceptibility to infants and children based mainly on the results of the developmental/reproductive toxicity studies. Exposure estimates are upper bound and will not underestimate exposure to butylate. Accordingly, the FQPA safety factor committee removed the 10x safety factor.

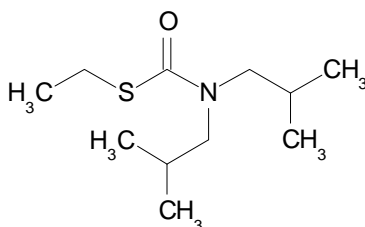
Based on the above mentioned endpoints, HED has selected reference doses (RfDs) for acute and chronic exposure for dietary risk assessments and calculated Population Adjusted Doses (PADs) which are the RfDs divided by the FQPA safety factors. Since the FQPA safety factor has been removed, the PAD is equal to the RfD. The PAD for acute effects (females 13+ only) is 0.4 mg/kg/day; for the general population (including infant and children), the acute PAD is 6 mg/kg/day. The PAD for chronic effects (general population) is equal to the chronic reference dose of 0.05 mg/kg bw/day.

No detectable residues were found in field trials. Results of the dietary analyses showed exposure to butylate consumed <1% of the chronic and acute PAD even when using conservative assumptions of tolerance level residues and 100% crop treated. Butylate is mobile to slightly mobile in soil. However, based on the vapor pressure and Henry's Law Constant, it is expected to dissipate primarily by volatilization. Significant residues of butylate are not expected to reach surface or ground water.

There are no registered residential uses at the present time. Consequently, an aggregate exposure assessment conducted for butylate included consideration of exposures from food and drinking water, only. Since the drinking water calculations were based on modeling estimates, Drinking Water Levels of Comparison (DWLOCs) were calculated. Upon comparison of the acute and chronic DWLOCs with the environmental concentrations of butylate estimated using conservative modeling, surface and ground water concentrations are less than the DWLOCs for all populations. Thus, there is no acute or chronic concern for drinking water from surface or groundwater sources.

2.0 PHYSICAL CHEMICAL PROPERTIES CHARACTERIZATION

The chemical name for Butylate is S-ethyl diisobutyl thiocarbamate. The chemical structure is



Other identifying characteristics and codes are:

Empirical Formula:	C ₁₁ H ₂₃ NOS
Molecular Weight:	217.4
CAS Registry No.:	2008-41-5
PC Code:	041405

Technical butylate is a pale yellow liquid with a boiling point of 107-109 °C (5 mm Hg) and a density of 0.94 g/mL. Butylate is soluble at less than 50 ppm in water at 20 °C. Butylate is miscible with acetone, acetonitrile, ethyl acetate, hexane, methanol, 1-octanol, and toluene. Butylate is highly volatile (vapor pressure = 13 x 10⁻³ mm Hg at 25° C) and is similar to the trialkylthiolcarbamates in both chemical and biological behavior.

3.0 HAZARD CHARACTERIZATION

3.1 Hazard Profile

Toxicology data are used by HED to assess the hazards to humans. The data are derived from a variety of acute, subchronic, and chronic toxicity tests; developmental/reproductive tests; and tests to assess mutagenicity and pesticide metabolism. The toxicity database for butylate adequately supports tolerance reassessment.

Acute toxicity values and toxicity categories for butylate (95.5-98.0%) are summarized in Table 1. The data indicate that butylate has low acute oral, dermal, and inhalation toxicity. It produced mild skin irritation (toxicity category IV) and no eye irritation. It was found to be a mild skin sensitizer.

Sufficient data are available to describe the subchronic toxicity of butylate. The available subchronic toxicity studies include 90-day feeding studies in rats and dogs and a 21-day dermal toxicity study in rabbits. In general, the data indicated that butylate did not produce significant toxicity with either 90-day oral or 21-day dermal administrations. Although the 90-day feeding studies in rats and dogs were found to be unacceptable, additional studies are not required since acceptable chronic feeding studies are available for both of these species.

Adequate data are available to assess the chronic toxicity and carcinogenic potential of butylate. The most consistent toxicological findings following chronic butylate exposure were decreased body weight and changes in the liver clinical pathology seen in mice (cellular infiltrates and focal necrosis), rats (hepatocellular hypertrophy and hepatocytomegaly) and dogs (hepatocellular vacuolation). Exposure to butylate also resulted in adverse kidney effects (amyloidosis, chronic nephritis, and lymphocytic foci) in mice. The available carcinogenicity data on rats and mice indicate that butylate is not carcinogenic. Butylate has been classified as a **Group E** "not likely" carcinogen (no evidence of carcinogenicity for humans).

Developmental studies in rats and rabbits, designed to identify possible adverse effects on the developing organism which may result from the in-utero exposure to the pesticide were also conducted. These studies in rats demonstrated that butylate induced a decrease in fetal weight and increased incidences of hematomas of thoracic spinal region and of misaligned sternebrae in Sprague-Dawley rats. No developmental effect was seen in rabbits.

The developmental toxicity studies showed no evidence of increased sensitivity or susceptibility of young rats or rabbits following pre- or postnatal exposure to butylate. In all studies, No Observable Adverse Effect Levels (NOAELs) were the same or higher for fetuses and offspring relative to parental animals.

The available reproduction data in rats showed that butylate did not affect mating behavior, conception, parturition, lactation, and weaning.

Butylate was negative for inducing mutations in all acceptable guideline studies of the standard battery of mutagenicity tests. Thus, in the Ames assay, butylate was negative for inducing reverse mutation in four histidine-requiring strains of Salmonella typhimurium at doses up to the limit of solubility (5 uL/plate) under both nonactivation and two sources of metabolic activation (rat and mouse S9). In the mouse lymphoma multiple endpoint test (forward mutation assay part), no increase in mutant colonies was found in mouse lymphoma cells treated with butylate up to levels producing excessive toxicity (relative cell survivals of 10-25%), in either the presence or absence of metabolic activation. In the cytogenetic portion of the mouse lymphoma multiple endpoint test (cytogenetic assay), butylate applied to mouse lymphoma cells induced dose-related sister chromatid exchanges under activation

conditions only, but no chromosome aberrations with or without activation up to toxic levels. The interpretation and biological significance of sister-chromatid exchanges are unknown at this time.

Butylate was also tested in accessory non-guideline studies, with negative results. Butylate failed to increase gene conversions in the D4 strain of the yeast, *Saccharomyces cerevisiae*, at either nonactivated or activated doses up to 5.0 uL/mL (limit dose). In the transformation assay, butylate was negative for the ability to transform BALB/3T3 cells, even at concentrations producing severe toxicity.

A total of three reports on the metabolism of butylate have been submitted. Together, the reported studies satisfy the metabolism data requirements for butylate. They indicate that with oral administration butylate is absorbed rapidly, metabolized, and eliminated. No evidence of bioaccumulation was observed and no metabolites which raised toxicological concern were identified.

The available acute neurotoxicity screening study showed that butylate at 2000 mg/kg produced clinical signs such as salivation, lachrymation, and tiptoe gait and induced neuronal cell necrosis in the brain and degeneration of the sciatic nerve. The subchronic neurotoxicity study employed substantially lower doses (~383 mg/kg, highest dose tested) relative to those of the acute neurotoxicity study and no neurotoxic effect was seen. Additionally, there were no compound-related changes recorded in brain, plasma or erythrocyte cholinesterase activities.

The toxicology profile of butylate is shown in Table 2 of this document.

Table 1: Acute Toxicity Data (butylate: 95.5-98.0%)*

TEST/ GLN	MRID/ Accession No.**	RESULTS	CATEGORY
Oral LD50--rat/81-1	254690	LD ₅₀ = 4850 mg/kg (males) LD ₅₀ = 4785 mg/kg (females)	III
Dermal LD50--rabbit/81-2	254690	LD ₅₀ > 5000 mg/kg (males and females)	IV
Inhalation LC50--rat/81-3	42389401	LC ₅₀ >1.64 mg/L	III
Eye irritation--rabbit/81-4	254690	No irritation	IV
Dermal irritation--rabbit/81-5	254690	Mild irritation	IV
Dermal sensitization--guinea pig/81-6	42123903	Moderate skin sensitizer	---

* It is noted that the acute toxicity data presented in this Table are derived from the studies conducted with Technical butylate (95.5-98.0% a.i.). However, some of the acute toxicity data (oral, dermal, eye irritation, and dermal irritation) presented in the original HED RED (dated 7/27/93) were derived from the studies conducted with Technical butylate (85.7% a.i.). It should also be noted that in the previous table, butylate with lower percentage a.i. had greater toxicity as reflected by lower LD₅₀ values.

** The 8 digit numbers are MRID No's; 6 digit numbers are Accession No's.

Table 2. Toxicology Profile for Butylate

Study Type (MRID No.)	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Additional Relevant Data	Core Grade
Subchronic Toxicity				
21 day dermal - Rabbit (MRID 00026312 and 07101608)	≥312 mg ai/kg	Not established	Butylate technical (labeled R-1910 6-E consisting 78% a.i.) was applied five days/week to normal (5/sex/group) and abraded (5/sex/group) skin sites of New Zealand White rabbits as a 20% solution of control blank (labeled Methyl Trithion TDE 1.5-2E), a 10% solution (156 mg ai/kg) and a 20% solution (312 mg ai/kg) (MRID 00026312 and 07101608). Each test animal received 2 ml/kg of the test article. No systemic effects were observed at the lowest or highest dose tested. Treated areas of both control and treated animals showed dermal irritation (erythema, dryness, fissuring, and sloughing). "Congestion" was reported in kidneys and lungs of treated animals, but no supportive histopathology for these observations was found by the investigators.	Acceptable
90-day feeding - Rat (MRID 00026313 and 07101609)	≥32 mg/kg/day	Not established	Technical butylate (no purity was given) was given to Charles River rats (15/sex/dose) in the diet at levels calculated to provide daily intakes of 8, 16, or 32 mg/kg/day for 21 days. No differences from controls were noted at any dose level in body weights, hematological, blood chemistry and cholinesterase values and gross organ effects. A more recent chronic (2-year) rat study has been found acceptable and the 90-day rodent data requirement is waived.	Unacceptable
90-day feeding - dog (MRID 00026314)	≥45 mg/kg/day	Not established	Groups of Beagle dogs (3/sex/dose) received butylate in the diet at doses of 0, 450, 900, or 1800 ppm (0, 11.25, 22.5, or 45 mg/kg/day) for 13 weeks. No significant differences from controls were noted at any dose level in behavior or body weight. The neurological, ophthalmological, hematological, blood chemistry, and cholinesterase (brain, red blood cells, and plasma) values were comparable to those of the controls. Additionally, neither gross organ appearance nor weight were affected by treatment, and microscopic necropsy findings were comparable in all groups. A more recent chronic (2-year) rat study has been found acceptable and the 90-day non-rodent data requirement is waived.	Unacceptable
Chronic Toxicity				
Chronic/carcinogenicity feeding study - Rat (MRID 00125678, 41014901 and 41249501)	50 mg/kg/day	100 mg/kg/day	The study demonstrated that butylate was not carcinogenic in rats at the doses tested (0, 50, 100, 200 or 400 mg/kg/day) . Effects seen at the LOAEL included only decreased body weight in both male and female rats. Effects seen at higher doses included increases in the combined incidence of periportal hepatocellular, hypertrophy and hepatocytomegaly in the livers of males. Incidences of lesions among treated females at any dose level were not significantly different from controls.	Acceptable

Study Type (MRID No.)	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Additional Relevant Data	Core Grade
Chronic toxicity - dog (MRID No. 40389101)	Males: 5 mg/kg/day Females: 25mg/kg/day	Males: 25 mg/kg/day Females: 100 mg/kg/day (HDT)	Gelatin capsules containing 0, 5,25, or 100 mg/kg/day of butylate technical (100% a.i.) was administered to Beagle dogs (5/sex/dose) for 12 months. Effects at the LOAEL were decreased body weight gain, changes in clinical pathology parameters and increased absolute and relative liver and thyroid/parathyroid weights.	Acceptable
Carcinogenicity - Mouse (MRID 0035844)	Females: 20 mg/kg/day Males: 80 mg/kg/day	Females: 80 mg/kg/day Males: 320 mg/kg/day (HDT)	Butylate technical (98% a.i.) was administered to CD-1 mice (60/sex/dose) in the diet at concentrations of 0, 20, 80, or 320 mg/kg/day for 24 months. Effects at the LOAEL were decrease in body weights and increased incidences of kidney findings in females (amyloidosis, chronic nephritis, and lymphocytic foci) and decreased food consumption, decreased kidney weights, and increased incidences of microscopic changes in kidney and liver in males.	Acceptable
Developmental Toxicity				
Developmental Toxicity - Rat (MRID 00131032)	Maternal tox: 40 mg/kg/day Develop tox. 40 mg/kg/day (HDT)	Maternal tox: 400 mg/kg/day Develop tox. 400 mg/kg/day	Butylate technical (98.2%) was administered to female Sprague-Dawley rats (26/dose) by oral intubation at doses of 0, 40, 400, or 1000 mg/kg/day from gestation days 6 through 20. Maternal LOAEL based on decreases in body weight, body weight gain, food consumption and an increase in relative liver weight. At higher doses, an increase in early resorption was observed Developmental LOAEL based on decreased fetal weights and increased incidences of hematomas of the thoracic spinal region and misaligned sternebrae. There was also an increased incidence of incompletely ossified sternebrae in the high dose fetuses	Acceptable

Study Type (MRID No.)	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Additional Relevant Data	Core Grade
Developmental Toxicity - Rabbit (MRID 00131032)	Maternal tox: 100 mg/kg/day Develop tox. \geq 500 mg/kg/day (HDT)	Maternal tox: 500 mg/kg/day Develop tox. Not determined	Butylate technical (99%) was administered to female New Zealand White rabbits (16/dose) by oral intubation at doses of 0, 10, 100, or 500 mg/kg/day from gestation days 7 through 19. Maternal LOAEL based on decreased body weight gain and food consumption and an increase in absolute and relative ovarian weights.	Acceptable
Reproductive Toxicity				

Study Type (MRID No.)	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Additional Relevant Data	Core Grade
2-generational reproduction -rats (MRID 00160548 and 00155519)	Parental toxicity: 10 mg/kg/day Reproductive tox. : 10 mg/kg/day	Parental toxicity: 50 mg/kg/day Reproductive tox.: 50 mg/kg/day	<p>Butylate technical (98.2% a.i.) was administered to Sprague-Dawley CD rats (25/sex/dose) in the diet at concentrations of 0, 200, 1000 or 4000 ppm (equivalent to \approx0, 10, 50, or 200 mg/kg/day, respectively).</p> <p>Parental LOAEL based on decreased food consumption, decreased body weights and increased liver weights (females only). At 4000 ppm, body weights of the parental animals of the Po generation were significantly lower (10-11% for males and 9-14% for females) compared to the controls. Also, body weights of the parental animals of the P1 generation were significantly lower (9-18% for males and 14-19% for females) compared to the controls. At this dose, food consumption of the parental animals of the Po and P1 generations were significantly lower (8-17% for males and 6-21% for females) compared to the controls at most of the reported time intervals. In addition, at this dose, there were decreased hematocrit values in Po males and females, decreased hemoglobin values in Po and P1 females, increased relative liver weights of Po males (13%), Po females (12%) and P1 females. Microscopically, there was an increased incidence of hepatocyte vacuolation in the P1 males.</p> <p>Reproductive LOAEL based on decreased pup weights and decreased absolute brain and kidney weights. At 4000 ppm, there was decreased litter size in the F1a, F2a, and F2b generations, decreased absolute kidney weights of F1b males (24%) and F1b females (21%), decreased absolute brain weights of F1b males (10%) and F1b females (8%), decreased kidney weights of F2c males (24%), increased relative liver weights of F2c males and females, increased incidence of dilated kidney (renal pelvis) and retinal folds in the F1b generation.</p> <p>The decreased absolute brain weights in weanlings at 1000 and 4000 ppm are considered to be due to decreases in the overall body weights in these pups because the brain weight decrease was slight and there was no evidence of treatment-related neurotoxicity in the chronic studies in dogs, rats, or mice. No changes in brain weight or histopathology (in nonperfused brain tissues) were observed in any of the guideline studies. In addition, no neurotoxic effect was observed in the subchronic neurotoxicity study in rats where slightly higher doses were tested. The HIARC had evaluated this issue twice and concluded that these data provide no clear indication of quantitative or qualitative increased susceptibility following <i>in utero</i> or postnatal exposure to butylate in the multigeneration reproduction study in rats.</p>	Acceptable
Mutagenicity				
Mutagenicity studies (MRID 00162707, 00162708, 00162709)	N/A	N/A	Butylate was negative for inducing mutations in all acceptable guideline studies of the standard battery of mutagenicity tests.	Acceptable
Metabolism				
Metabolism studies (MRID 41037301, 00043680, 00129397)	N/A	N/A	With oral administration, butylate is absorbed rapidly, metabolized, and eliminated. No evidence of bioaccumulation was observed and no metabolites which raised toxicological concern were identified	Acceptable

Study Type (MRID No.)	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Additional Relevant Data
Neurotoxicity			
Acute neurotoxicity screening study (MRID 43514101 and 43967901)	600 mg/kg	2000 mg/kg (HDT)	Butylate technical (95.7% a.i.) in corn oil was administered to Sprague-Dawley rats by gavage at single doses of 0, 200, 600, or 2000 mg/kg. LOAEL based on neuronal cell necrosis, body weight decrease, and clinical signs of toxicity.
Subchronic neurotoxicity screening battery (MRID 43452201)	≥ 5000 ppm (HDT) ≥ 366.1 mg/kg/day males ≥ 382.5 mg/kg/day females	not determined	Butylate (95.7% a.i.) was administered to APfSD rats (12/sex/dose) in the 250, 1000 or 5000 ppm for 13 weeks (0, 18.7, 76.0, or 366.1 mg/kg/day for males, 0, 18.7, 76.0, or 366.1 mg/kg/day for females, respectively). No evidence of functional (FOB/LA) impairment of the nervous system was found up to the highest dose tested (5000 ppm).

NOAEL = No Observable Adverse Effect Level

LOAEL = Lowest Observable Adverse Effect Level

LDT = Lowest Dose Tested; HDT = Highest Dose Tested

3.2 Dose Response Assessment and Hazard Endpoint Selection

The strengths and weaknesses of the butylate toxicology database were considered during the process of toxicity endpoint and dose selection. In general, all the required guideline studies on butylate were available and provided reasonable confidence when the toxicity endpoints and doses for risk assessment were selected. Based on the evaluation of the above summarized studies, the Hazard Identification Assessment Review Committee (HIARC) identified the toxicity endpoints and the dose levels for use in risk assessment (HIARC document of 6/9/98). The selected toxicity endpoints are summarized in Table 3. It should be noted that the HIARC did not use the 21-day dermal toxicity study in rabbits because: 1) only two dose levels were tested in the study; 2) a LOAEL was not established (i.e., the highest dose tested was not adequate to assess dermal or systemic toxicity); and 3) the concern for the developmental effects seen in the rat developmental toxicity study which were not evaluated in the 21-day dermal study. Information on risk assessment endpoints for other than dietary risk are included only for informational purposes - worker and residential risk assessments are not required for this tolerance reassessment.

Table 3. Summary of Toxicology Endpoint Selection

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary (Female 13+)	Developmental NOAEL=40	LOAEL = 400 mg/kg/day based on decreased fetal weights and increased incidences of misaligned sternebrae	Developmental-rat
	UF=100	Acute RfD = 0.4 mg/kg/day Acute PAD = 0.4 mg/kg/day	
Acute Dietary (General population)	Acute neurotoxicity NOAEL=600	LOAEL = 2000mg/kg based on sciatic nerve degeneration, neuronal cell necrosis, body weight decrease, and clinical signs of toxicity	Acute neurotoxicity-rat
	UF=100	Acute RfD = 6 mg/kg/day Acute PAD = 6 mg/kg/day	
Chronic Dietary	NOAEL=5	LOAEL = 25 mg/kg/day based on increased relative liver weight in male dogs	12-Month feeding-dog
	UF=100	Chronic RfD = 0.05 mg/kg/day Chronic PAD = 0.05 mg/kg/day	
Short-Term (a) (Dermal)	Developmental NOAEL=40	LOAEL = 400 mg/kg/day based on decreased fetal weights and increased incidences of misaligned sternebrae	Developmental-rat
Intermediate-Term (Dermal)	Developmental NOAEL=40	LOAEL = 400 mg/kg/day based on decreased fetal weights and increased incidences of misaligned sternebrae	Developmental-rat
Long-Term (Dermal)	None	Not required under the registered use patterns	
Inhalation (short & intermediate)	Developmental NOAEL=40	LOAEL = 400 mg/kg/day based on decreased fetal weights and increased incidences of misaligned sternebrae	Developmental-rat
Inhalation (long)	None	Not required under the registered use patterns	

a = Since an oral NOAEL was selected, a dermal absorption factor of 100% (default value) should be used in route-to-route extrapolation.

b = Since an oral NOAEL was selected, an inhalation absorption factor of 100% (default value) should be used in route-to-route extrapolation.

3.3 FQPA Considerations

The FQPA Safety Factor committee addressed the potential enhanced sensitivity of infants and children from exposure to butylate as required by the FQPA of 1996. In the prenatal developmental toxicity studies in rats and rabbits and the two-generation reproduction study in rats, toxicity to the offspring occurred at equivalent or higher doses than in maternal animals. It was determined that the available studies indicated no increased susceptibility of rats or rabbits to *in utero* and/or postnatal exposure to Butylate. (*Memorandum*: P.Chin to V. Dobozy dated June 25, 1998; HED Doc. No. 012729).

It should be noted that in the two-generational reproduction study in rats, the decreased absolute brain weights in weanlings at 1000 and 4000 ppm are considered to be due to decreases in the overall body weights of these pups because the brain weight decrease was slight and there was no evidence of treatment-related neurotoxicity in the chronic studies in dogs, rats, or mice. No changes in brain weight or histopathology (in nonperfused brain tissues) were observed in any of the guideline studies. In addition, no neurotoxic effect was observed in the subchronic neurotoxicity study in rats where much higher doses were tested. The HIARC had evaluated this issue twice and concluded that these data provide no clear indication of quantitative or qualitative increased susceptibility following *in utero* or postnatal exposure to butylate in the multigeneration reproduction study in rats.

Thus the FQPA Safety Factor Committee (B. Tarplee and J. Rowland, 8/27/98) recommended that the 10x Safety Factor should be removed since: 1) the toxicology data base is complete; 2) the developmental and reproductive toxicity data did not indicate increased sensitivity or susceptibility of rats or rabbits to *in utero* and/or postnatal exposure; 3) unrefined dietary exposure estimates (assuming all commodities contain tolerance level residues) will overestimate dietary exposure; 4) modeling data are used for ground and surface source drinking water exposure assessments resulting in estimates considered to be upper-bound concentrations; and 5) there are currently no registered residential uses for Butylate. Additionally, there is no evidence to support a recommendation for a developmental neurotoxicity study.

4.0 EXPOSURE ASSESSMENT

4.1 Summary of Registered Uses

Butylate (S-ethyl diisobutylthiocarbamate) is a selective herbicide registered for use on field corn, sweet corn, and popcorn. The chemical is formulated as an emulsifiable concentrate (EC) and as granules. All formulations are soil incorporated to prevent volatilization of the active ingredient. Applications may be made preplant, at planting, postplant, postemergence, and at fall before the ground freezes using conventional spray equipment or in center pivot irrigation systems (*Source: LUIS General Chemical Draft Report for Butylate*, 9/28/98). Butylate in the past has also been formulated with atrazine but that formulation has been phased out. Butylate was not produced in 1998 and usage and production are expected to continue declining. (Quantitative Usage Analysis for Butylate, S. Smearman, 2/5/99)

4.2 Dietary Exposure and Risk Assessment

4.2.1 Dietary Exposure from Food Sources

Tolerances for residues in or on food and feed commodities are expressed in terms of butylate per se [Source: 40 CFR §180.232]. Currently, only tolerances of 0.1 ppm for corn commodities have been established. These commodities include corn grain (including popcorn), fresh corn (including sweet corn; kernels plus cobs with husks removed), and corn forage and fodder (including sweet corn, field corn, and popcorn).

The qualitative nature of the residue in corn is adequately understood. The parent compound butylate is the residue of concern. The qualitative nature of the residue in animals is also adequately understood. Studies with rats indicate that >99% of administered [¹⁴C]butylate is rapidly metabolized to water-soluble compounds which are readily eliminated by excretion (in urine and feces). Because of the limited potential exposure to residues of butylate on livestock feed items, and lack of evidence that terminal residues of butylate exist in laboratory animals, data from ruminant and poultry metabolism studies have not been required. There is no reasonable expectation of finite residues of butylate in meat, milk, poultry, and eggs.

An adequate enforcement method is available for the enforcement of butylate tolerances. The enforcement method (Method A of PAM Vol. II; Sec. 180.232) is a GLC method with microcoulometric detection and a limit of detection of 0.04 ppm. It has undergone successful Agency method validation on corn grain. It was noted during the Agency-conducted method validation that resolution could be improved if flame ionization or flame photometric detection was used instead of microcoulometric detection. Since no livestock tolerances have been established for residues of butylate in animal commodities, enforcement methods for residues of butylate in animal commodities are not required.

The available residue data from crop field trials provide sufficient information to reassess the 0.1 ppm tolerances for residues of butylate in/on corn grain, fresh corn, and corn forage/fodder. Residues of butylate in or on about 250 samples of corn grain or whole ears and about 200 samples of field corn forage and fodder were nondetectable (<0.02 to <0.05 ppm). Corn grain and sweet corn cannery waste processing studies indicate that residues of butylate do not concentrate in processed food/feed items.

4.2.2 Dietary Risk from Food Sources

HED conducts dietary risk assessments using the Dietary Exposure Evaluation Model (DEEM™ Version 7.075), which incorporates consumption data generated in USDA's Continuing Surveys of Food Intakes by Individuals (CSFII), 1989-1992. For acute dietary risk assessments, the entire distribution of consumption events for individuals is combined with either a single residue level (deterministic analysis, risk at

95th percentile of exposure reported) or a distribution of residues (probabilistic analysis, referred to as ‘Monte Carlo,’ risk at 99.9th percentile of exposure reported) to obtain a distribution of exposure in mg/kg/day. For chronic dietary risk assessments, the three-day average of consumption for each sub-population is combined with average residues in commodities to determine average exposures in mg/kg/day.

Tier 1 analyses were conducted for both chronic and acute assessments. Tier 1 assessments were conducted using tolerance level residues and 100% crop treated (%CT). The analyses show that acute dietary exposure and risk are not of concern for all population subgroups considered. The estimated exposure at the 95th percentile in the Tier 1 assessment consumed < 1% of the acute Population Adjusted Dose (aPAD). Likewise, chronic dietary exposure and risk were not of concern with less than 1% of the chronic Population Adjusted Dose (cPAD) consumed for all population subgroups. A summary of the butylate acute and chronic dietary risk estimates are shown in Table 4.

These assessments are considered to be conservative since they are based on tolerance level residues and 100% CT.

Table 4. Summary of Butylate Acute and Chronic Dietary Exposure and Risk Estimates.

Population Subgroup	Chronic Assessment ¹		Acute (95th %ile) ²	
	Exposure (mg/kg/day)	% cPAD	Exposure (mg/kg/day)	% aPAD
General US Population	0.000150	<1	0.000475	<1
All infants	0.000310	<1	0.000905	<1
Children 1-6 years	0.000353	<1	0.000961	<1
Children 7-12 years	0.000266	<1	0.000663	<1
Females 13-50 years	0.000110	<1	0.000309	<1
Males 13-19 years old	0.000142	<1	0.000383	<1
Males 20+ years old	0.000085	<1	0.000250	<1
Seniors 55+	0.000068	<1	0.000205	<1

1. The chronic PAD (cPAD) is 0.05 mg/kg/day for all subgroups
2. The acute PAD is 0.4 mg/kg/day for females 13+ and 6 mg/kg/day for the general U.S. population including infants and children.

4.2.3. Dietary Exposure from Water Sources

The environmental fate data base for butylate is incomplete. Preliminary data, however, indicate that butylate is mobile to moderately mobile in soil so that the runoff to surface water following a rainfall event is possible when butylate is applied as a preemergence herbicide or shortly after planting. The parent compound dissipates primarily by volatilization from soil and once in the atmosphere, butylate may be transported in fogs, mists, and rainwater.

Although both ground and surface water monitoring data are available from areas where butylate is applied to corn (USGS/NAWQA), the Environmental Fate and Effects Division (EFED) recommends that modeling estimates be used for both surface and ground water in exposure assessments since there is currently no standard procedure for determining acute and chronic values from monitoring data. Estimated Environmental Concentrations (EECs) have been calculated for ground and surface water based on the current EFED first level screening models, SCI-GROW and GENEEC respectively. For surface water, the maximum concentration of 33.1 ug/L and the 56-day EEC of 29.8 ug/L was used for acute and chronic risk calculations, respectively. For ground water, the SCI-GROW2 concentration of 0.41 ug/L for butylate was used for both acute and chronic risk assessment. This information was obtained from a memorandum dated 8/18/98 (J. Breithaupt, EFED, D248420).

Concentrations of butylate reported in both surface water and ground water monitoring data are lower than the levels in the environment predicted using GENEEC and SCI-GROW2.

4.2.4. Dietary Risk from Water Sources

HED has calculated drinking water levels of comparison (DWLOCs) for acute and chronic exposure to butylate in surface and groundwater which are presented in Tables 6 and 7. The $DWLOC_{acute}$ is the concentration in drinking water as a part of the aggregate acute exposure that occupies no more than 100% of the acute PAD. Typically, to calculate the DWLOC for acute exposure relative to an acute toxicity endpoint, the acute dietary food exposure (from the DEEM™ analysis) is subtracted from the acute PAD. The $DWLOC_{chronic}$ is the concentration in drinking water as a part of the aggregate chronic exposure that occupies no more than 100% of the chronic PAD when considered together with other sources of exposure. To calculate the DWLOC for chronic exposure relative to a chronic toxicity endpoint, the chronic dietary food exposure (from DEEM™) was subtracted from the chronic PAD to obtain the acceptable chronic exposure to butylate in drinking water. DWLOCs were then calculated using default body weights and drinking water consumption figures. Assumptions used in calculating the DWLOCs include 70 kg body weight for the U.S. population, 60 kg body weight for adult females, 10 kg body weight for children, two liters of water consumption per day for adults, and one liter consumption for children.

Table 5. Butylate - Summary of Chronic DWLOC Calculations

Population Subgroup	cPAD (mg/kg/day)	Food Exposure (mg/kg/day)	Available Water Exposure (mg/kg/day)	DWLOC ($\mu\text{g/L}$)	EFED Generated EECs	
					Surface Water (Overall mean) ($\mu\text{g/L}$)	Ground Water (SCI-GROW) ($\mu\text{g/L}$)
U.S. Population	0.05	0.000150	0.04985	1745	$29.8 \div 3 \approx 10$	0.41
Females 13-50 yrs	0.05	0.000110	0.04989	1497	$29.8 \div 3 \approx 10$	0.41
Children 1-6 yrs	0.05	0.000353	0.04965	497	$29.8 \div 3 \approx 10$	0.41
All Infants	0.05	0.000310	0.04969	497	$29.8 \div 3 \approx 10$	0.41

EEC = Estimated Environmental Concentrations

Butylate surface water EECs are from GENEEC modeling; it is the policy of HED to divide GENEEC modeling numbers by 3 for comparison to chronic DWLOC.

$\text{DWLOC} = \frac{\text{water exposure} \times \text{body weight}}{\text{Liters of water} \times 10^{-3}}$ where water exposure = cPAD - food exposure

Body weight = 70 kg for U.S. Population, 60 kg for females, 10 kg for infants and children
Liters of water = 2L for Adults and 1L for infants and children

Table 6. Summary of Acute DWLOC Calculations

Population Subgroup	aPAD (mg/kg/day)	Food Exposure (mg/kg/day)	Available Water Exposure (mg/kg/day)	DWLOC ($\mu\text{g/L}$)	EFED Generated EECs	
					Surface Water ($\mu\text{g/L}$)	Ground Water ($\mu\text{g/L}$)
U.S. Population	6.0	0.000475	6.0	210000	33.1	0.41
Females 13-50 yrs	0.4	0.000309	0.4	12000	33.1	0.41
Children 1-6 yr	6.0	0.000961	6.0	60000	33.1	0.41
All Infants	6.0	0.000905	6.0	60000	33.1	0.41

EEC = Estimated Environmental Concentrations

$\text{DWLOC} = \frac{\text{water exposure} \times \text{body weight}}{\text{Liters of water} \times 10^{-3}}$ where water exposure = aPAD - food exposure

Body weight = 70 kg for U.S. Population, 60 kg for females, 10 kg for infants and children
Liters of water = 2L for Adults and 1L for infants and children

Upon comparison of the acute and chronic DWLOCs with the estimated EECs of butylate

estimated using conservative modeling, surface and ground water concentrations are considerably less than the DWLOCs (Tables 5 and 6) for all populations. Consequently, there is no acute or chronic concern for drinking water from surface or groundwater sources.

4.3 Residential Exposure

There are no products containing butylate as an active ingredient that are registered for use in a residential or other non-occupational setting. Therefore, there is no need to conduct a residential exposure and risk assessment.

Spray drift is always a potential source of exposure to residents nearby to spraying operations. This is particularly the case with aerial application, but, to a lesser extent, could also be a potential source of exposure from groundboom application methods. The Agency has been working with the Spray Drift Task Force, EPA Regional Offices and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices. The Agency is now requiring interim mitigation measures for aerial applications that must be placed on product labels/labeling. The Agency has completed its evaluation of the new data base submitted by the Spray Drift Task Force, a membership of U.S. pesticide registrants, and is developing a policy on how to appropriately apply the data and the AgDRIFT computer model to its risk assessments for pesticides applied by air, orchard airblast and ground hydraulic methods. After the policy is in place, the Agency may impose further refinements in spray drift management practices to reduce off-target drift and risks associated with aerial as well as other application types where appropriate.

5.0 AGGREGATE RISK ASSESSMENT AND RISK CHARACTERIZATION

5.1 Aggregate Risk Assessment

FQPA requires an aggregate risk assessment to be conducted considering all non-occupational sources, including exposure from water, food, and residential use. Since there are no registered residential uses, an aggregate exposure assessment for butylate includes consideration of exposures from food and drinking water. Since the drinking water calculations were based on modeling estimates, Drinking Water Levels of Comparison (DWLOCs) were calculated. The DWLOC is the concentration of a chemical in drinking water that would be acceptable as an upper limit in light of *total* aggregate exposure to that chemical from food, water, and non-occupational (residential) sources. Acute and chronic DWLOCs for butylate were calculated based on dietary risk assessments using tolerance level residues in food. These are presented in Tables 5 and 6 in this document. Comparisons are made between DWLOCs and the estimated concentrations of butylate in surface water and ground water generated via GENEEC and SCI-GROW, respectively. If the model estimate is less than the DWLOC, there is generally no drinking water concern. Results showed that surface and ground water concentrations are considerably less than the DWLOCs for all populations. Consequently, there is no acute or chronic concern for drinking water from surface or groundwater sources.

5.2 Cumulative Exposure To Substances with Common Mechanism of Toxicity.

The Food Quality Protection Act requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity." The Agency is examining whether and to what extent some or all organophosphorous and carbamate (including, but not limited to, methyl carbamate, N-methyl carbamate, thiocarbamate, and dithiocarbamate) pesticides may share acetylcholinesterase inhibition as a common mechanism of toxicity. In contrast to the methyl and N-methyl carbamates, the Agency has a less fully developed understanding of whether the thiocarbamates share acetylcholinesterase inhibition as a common mechanism of toxicity with other cholinesterase-inhibiting chemicals. While current data are limited, the thiocarbamates appear to be comparatively weak cholinesterase inhibitors and are generally regulated based on other toxic endpoints. As a result, currently the Agency has not determined if it would be appropriate to include them in a cumulative risk assessment with other such chemicals (e.g., the organophosphorous and carbamate pesticides) [see the August 31, 1999, EPA Memorandum entitled *September 1999 Meeting of the FIFRA Science Advisory Panel: Working Documents for the Session: "Proposed Guidance for Conducting Cumulative Hazard Assessments for Pesticides that Have a Common Mechanism of Toxicity"* and *"The Carbamate Pesticides and the Grouping of Carbamate with the Organophosphorous Pesticides"*]. Also see 40 CFR section 180.3(e)(5), which presents the Agency's initial grouping of chemicals that would be considered together for the purpose of tolerance reassessment. This grouping includes some carbamate pesticides, but not thiocarbamate pesticides as members of the class of acetylcholinesterase-inhibiting compounds. In September 1999, the Agency presented a paper (cited above) on the common mechanism of toxicity of the carbamate pesticides to the Science Advisory Panel (SAP). In that presentation, the Agency noted that although various classes of compounds may inhibit acetylcholinesterase, the potency, reversibility, and related factors may influence whether or not related pesticides should be included in a cumulative risk assessment.

Therefore, for the purposes of this risk assessment, the Agency has assumed that butylate does not share a common mechanism of toxicity with cholinesterase-inhibiting chemicals.

5.3 Endocrine Disruption

The Agency is required under the FFDCA, as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there was scientific bases for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help

determine whether a substance may have an effect in humans, FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

When the appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, butylate may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption.

6.0 TOLERANCE REASSESSMENT RECOMMENDATIONS

6.1 Tolerance Reassessment Recommendation

HED has sufficient residue data for reassessing the tolerances in/on field corn grain (including popcorn), sweet corn kernels plus cob with husk removed (K+CWHR), field corn forage and fodder (including popcorn), and sweet corn forage and fodder. Tolerance for residues of butylate in meat, milk, poultry, and eggs are not required. The registered uses of butylate are classified as category 3 of 40 CFR §180.6(a) with respect to residues in meat, milk, poultry, and eggs. Based on the residue data submitted, no changes in the current tolerances are required. A summary of butylate tolerances are presented in Table 7.

Table 7. Summary of Butylate Tolerance Reassessments

Commodity	Current Tolerance (ppm)	Tolerance Reassessment (ppm)
<i>corn, field, grain</i> <i>corn, pop, grain</i>	0.1	0.1
<i>corn, sweet (K + CWHR)</i>	0.1	0.1
<i>corn, field, fodder</i> <i>corn, field, forage</i> <i>corn, pop, fodder</i> <i>corn, pop, forage</i> <i>corn, sweet, forage</i>	0.1	0.1

6.2 Codex/International Harmonization

No maximum residue limits (MRLs) for butylate have been established or proposed by Codex for any agricultural commodity. Therefore, no compatibility questions exist with respect to U.S. tolerances.

7.0 DATA NEEDS

No additional data are required.

cc: List A Rereg. File, B. Gregg(SRRD)
RDI: WPhang 2/26/01, RARC 2/6/2001
7509C:FFort:RRB1:CM2:Rm 722H:703 305-7478:2/26/2001

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